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Complex Formation of Inorganic Salts with β-Cyclodextrin

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Abstract. The interactions between some alkali halides, perchlorates and sulfates and β-cyclodextrin (cycloheptaamylose, CD) have been investigated by solubility, spectrophotometric, thermoanalytical and preparative methods. The main conclusions are as follows. (i) The most pronounced interaction occurs with the anions; in dilute solutions this can be characterized as the formation of 1 : 1 complexes. In more concentrated solutions ternary associates and more complicated ones (involving the cations as well) are also formed. (ii) Changes in the activity coefficients or of the activity of water may also have some role in the phenomena, but it cannot be dominant: differences according to the individual properties of the anions are much more pronounced than to those of the cations or to changes of the ionic strength. (iii) Regarding the type of complex formation, real inclusion and 'outer sphere' interactions (via hydrogen bonds) are also probable.

Key words. inclusion and outer sphere complexes, photometry, coprecipitation

1. Introduction

Cyclodextrins are cyclic oligosaccharides having the ability to form inclusion complexes with a great variety of different guest molecules. The annular cavity of the CD is mainly hydrophobic but with a relatively high electron density, owing to the lining with the methine groups and the interglucosidic ether-like O(4) atoms [1]. At the same time, the alcoholic OH-groups are pointing away from the cavity and they may contribute to 'closing the cage' or to intermolecular associations by hydrogen bonding.

In a previous communication [2] we reported on the complex formation of β-cyclodextrin (cycloheptaamylose, hereafter CD) with some inorganic anions. This work has now been extended by some further experimental studies and on further systems and we try to give an explanation of the rather complicated phenomena.

The investigations were initiated by the technological observation that the solubilities and precipitation of the cyclodextrins and their inclusion complexes are influenced by some inorganic salts, sometimes depending on their concentrations [1, 3].

There are rather few data in the literature concerning the equilibria in solutions, and there are large inconsistencies between the different results and especially between the interpretations. Sulfate, phosphate and fluoride ions are regarded by some authors [4, 5] as totally indifferent, others have noted their decreasing effect on the apparent dissociation constants of some inclusion complexes but this is

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attributed only to the changes in ionic strength [6, 7]. Similarly, the assumptions concerning the forces contributing to the interactions and the hydration state of the anions in the complexes are rather different [5–8].

In our work, (i) as the most simple systems, the effect of some alkali halides, perchlorates and sulfates was studied on the solubility of β-CD. (ii) The equilibria in aqueous solutions were investigated spectrophotometrically based on competing reactions between the salts and the inclusion complexes of β-CD with phenolphthalein [9] and methyl orange, and by following the effect of salts on the formation of the β-CD–benzoic acid complex. (iii) As a third line, β-CD itself and its complex with benzoic acid was crystallized in the presence of different salts, and an attempt has been made to interpret the results obtained by the different methods in a comprehensive way.

2. Experimental

2.1. MATERIALS

The β-cyclodextrin was produced by the Chinoin Chemical-Pharmaceutical Works (Budapest, Hungary) and was recrystallized from water twice.

Benzoic acid was used after recrystallization from water. The indicators (phenolphthalein and methyl orange) were Reanal products of analytical grade and no impurities could be detected. All the other materials were of analytical grade.

2.2. SOLUBILITY MEASUREMENTS

The solubility measurements were carried out as follows. β-CD was added in small excess to solutions of different salt concentrations measured into volumetric flasks. The flasks were thermostatted at $25.0 \pm 0.1°C$ and filled up to the mark after most of the CD had been dissolved. The solutions containing minute amounts of undissolved CD were stored in a thermostat and shaken frequently until equilibrium was reached (at least 2 days). The concentration of the dissolved CD was determined by optical rotatory measurements using a ZEISS Polamat A instrument at the wavelength of 366 nm in a 1 dm thickness cell. A plot of rotation vs. CD concentration between $0–1.5 \times 10^{-2}$ mol dm^{-3} concentrations was linear with a slope of 536.7 ± 1.4 grade dm^3 mol^{-1}. In the presence of the studied salts the slope was the same up to their 2 mol dm^{-3} concentration.

In another type of experiment the solubility of benzoic acid was measured in solutions of different CD concentrations [10] also containing the salts under investigation. The concentration of β-CD was varied between 0 and 1.5×10^{-2} mol dm^{-3} and those of the salts between 0 and 1 or 2 mol dm^{-3}.

The spectrophotometric method was based on the fact that the complex formation of some indicators with β-CD are accompanied by a significant colour change, and if a third component is present, its complex formation can be followed through the change in the indicator reaction. (The method using phenolphthalein is described in detail in Refs. 2, 9 and 11.) The concentration of phenolphthalein was 3×10^{-5} mol dm^{-3}, pH = 10.5 (2×10^{-2} mol dm^{-3} Na_2CO_3); the concentration of β-CD was 2×10^{-5}–3×10^{-3} mol dm^{-3} and those of the salts were 0.01–2 mol dm^{-3}. In the case of ammonium salts, an acidic medium must be used, therefore methyl orange was used as the competing reagent in solutions of pH = 2.6 (4×10^{-2} mol dm^{-3} formic acid). The concentration of the indicator was 2×10^{-5} mol dm^{-3} and that of the CD 10^{-4}–6×10^{-3} mol dm^{-3}. The absorbance was measured at 520 nm.

2.3. CRYSTALLIZATION EXPERIMENTS AND PREPARATION OF THE β-CD-BENZOIC ACID COMPLEX

Pure β-CD (5 g per 100 g of water) or β-CD and benzoic acid, respectively, were dissolved in hot distilled water or in solutions containing the salts under investigation in concentrations of 2.00 mol/1 kg water (or 0.5 mol/1 kg water in one series), then the solutions were allowed to cool down slowly under vigorous stirring. In the case of the preparation of the complex, the initial molar ratio (benzoic acid/CD in the solutions) was 0.78–1.12. The temperature at the beginning of crystallization was registered, the amount of solid phases precipitated by room temperature was weighed and their compositions were determined by classical methods of analytical chemistry.

X-ray powder diagrams were recorded and interpreted in the Physical-Chemical Research Laboratory of the Chinoin Works by Dr. K. Simon.

TG, DTG and DTA diagrams of the solid phases were recorded on a Paulik-Paulik-Erdey type derivatograph, using 50 mg samples and a heating rate of 2°C/min in air.

3. Results

The most typical results characterizing the solubility changes of β-CD caused by different salts are summarized in Figures 1 and 2. The effect of $LiClO_4$ is similar to but even more pronounced than that of $NaClO_4$, and the solubility is also decreased by ammonium sulfate, similar to the effect of sodium sulfate.

It is remarkable that the solubility increasing effect is linear only in the case of NaCl and, except for the NaCl/LiCl mixtures, deviations from linearity remain even if the ionic strength is constant.

The results obtained in the solubility measurements and those connected with the compositions and properties of the solid phases prepared separately, can be summarized as follows.

1. In the presence of sodium sulfate and ammonium sulfate, the solubility of the pure CD is decreased, accordingly, the amount of the precipitated benzoic acid complex is increased but this latter effect is somewhat smaller. Inorganic salts could not be detected in the solid phases in either case.

2. Sodium perchlorate increases the solubility both in the case of pure CD and of the benzoic acid-CD complex, but again, the effect on the pure CD exceeds that on the complex. In both cases the solid phase contain significant and reproducible amounts of the salt: 0.7 mole $NaClO_4$/1 mole CD in itself, and in the complex CD : benzoic acid : $NaClO_4$ = 1 : 1 : 0.5.

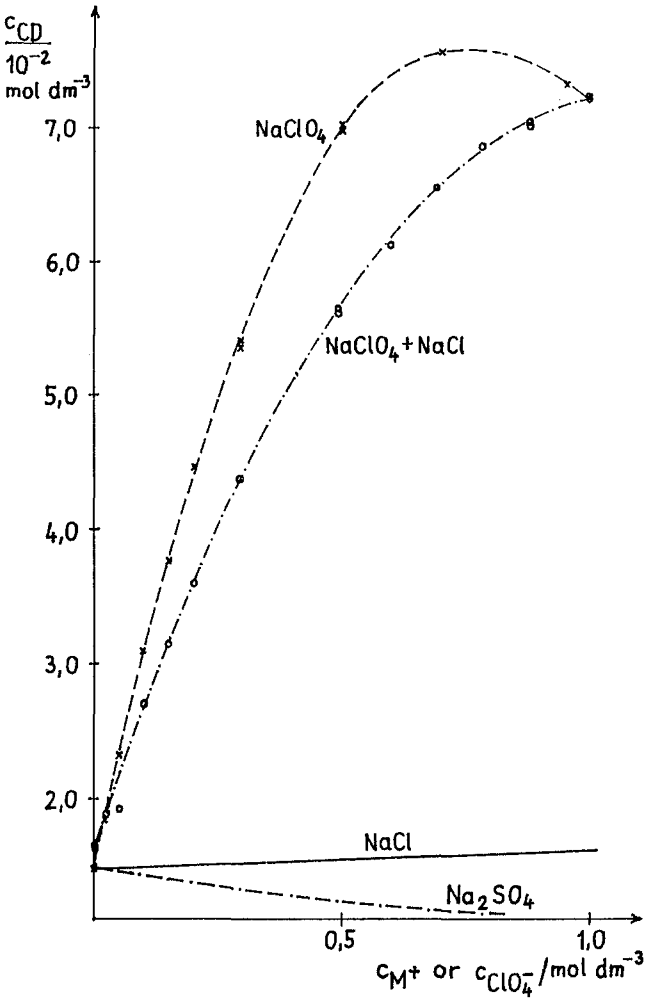

Fig. 1. The solubility changes of β-CD caused by some inorganic salts. (-o-·-o-· : $NaClO_4 + NaCl$ in a constant total concentration of 1.0 mol dm^{-3})

3. The role of sodium chloride is the most inconsistent: in contrast to the solubility increasing effect on the pure CD, precipitation of the benzoic acid complex is somewhat promoted. Some incorporation of the salt can be detected but it is not so characteristic as in the case of sodium perchlorate.

4. The benzoic acid content of the solid complexes was always found to be 1 mole acid/1 mole CD, practically independently of the compositions of the initial solutions. (The only exceptions are those prepared in the presence of sulfates where the composition of the solid phase is approximately equal to that of the solution when the acid content of the solution is less than that according to the 1 : 1 molar ratio.)

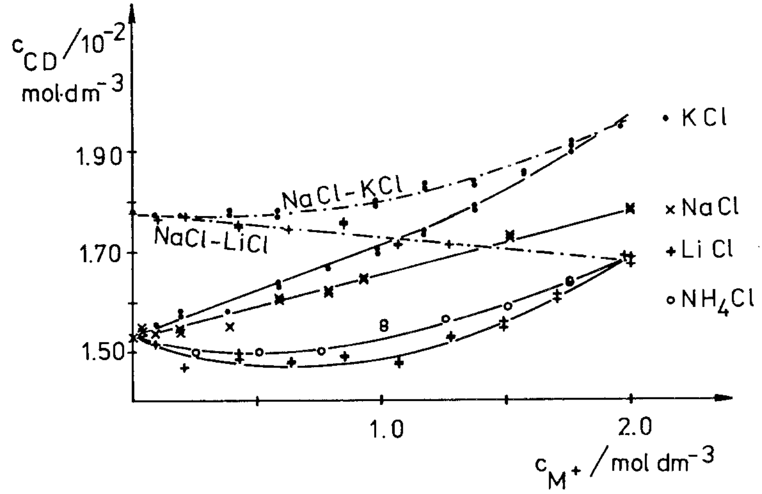

Fig. 2. The solubility changes of β-CD in the presence of some chlorides. (-·-·- : the total concentration is constant, the concentration marked refers to that of the second component)

The sodium and ammonium sulfates have different effects on the thermal behaviour of precipitates than on the solubility and stoichiometry mentioned above: sodium sulfate seems to stabilize the structure against decomposition, while the materials crystallized from solutions containing ammonium sulfate start to decompose at lower temperature and this decomposition is rather slow in spite of the fact that no detectable amounts of the salts are incorporated.

In contrast, according to the X-ray power diagrams, significant differences in the structure are detected only in the case of the incorporation of benzoic acid and/or sodium perchlorate. It is, however, not impossible that the more complex and slightly different intermolecular interactions existing in the concentrated solutions or especially in the transition state preceding crystallization may result in slightly modified interactions in the – essentially similar – solid structures and this may lead to easier or more hindered formation and release of water molecules which is the starting step of decomposition.

The concentration of dissolved benzoic acid is increased practically proportionally with increasing concentration of β-CD, but the slope is over 1, $\tan\alpha = 1.05$. It follows that the benzoic acid (HB) forms with CD not only a 1 : 1 but also a 2 : 1 complex [10], and the slope can be described as

$$\tan\alpha = \frac{[\mathrm{HB}] + [\mathrm{HB{\cdot}CD}] + 2[(\mathrm{HB})_2{\cdot}\mathrm{CD}]}{[\mathrm{CD}] + [\mathrm{HB{\cdot}CD}] + [(\mathrm{HB})_2{\cdot}\mathrm{CD}]}.$$

The benzoic acid concentration vs cyclodextrin concentration plots give straight lines in the presence of salts (added in constant concentration in every series of measurements) but the slope is strongly modified by the presence of different salts, as shown in Figure 3. These results cannot be evaluated quantitatively in a direct way because of the fact that species with different stoichiometries are formed, therefore they are used only for qualitative comparisons.

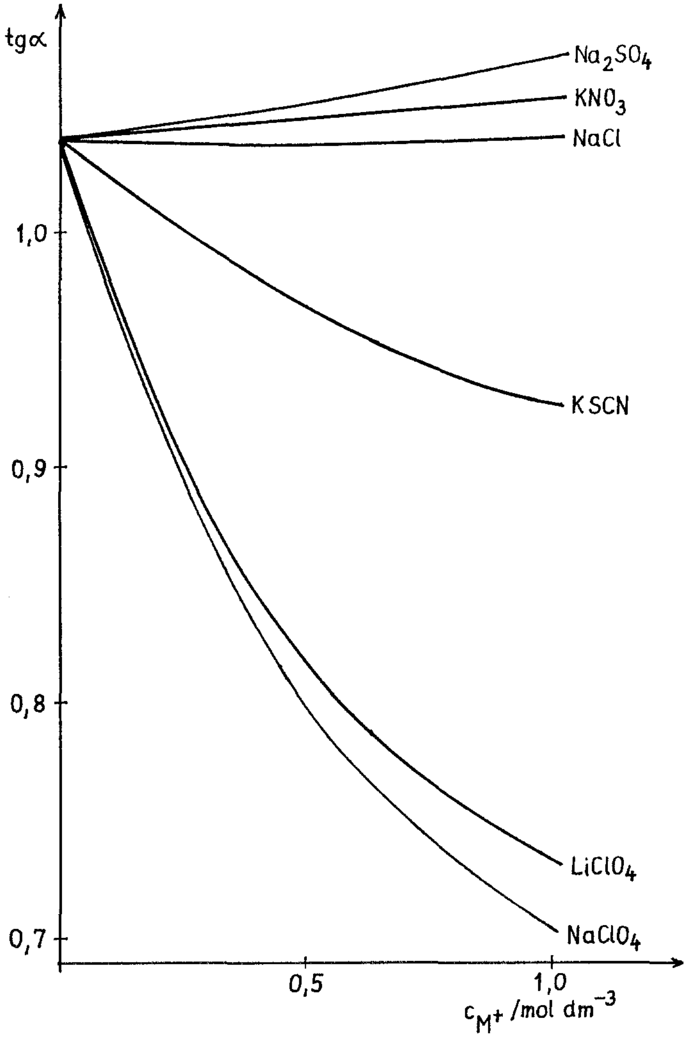

Fig. 3. The influence of salts on the solubility increasing effect of β-CD on benzoic acid. (tg α refers to the solubility of benzoic acid vs. CD-concentration plots)

The equilibria can be better characterized by the spectrophotometric investigations carried out in dilute solutions. The results of measurements using phenolphthalein as a competing reagent have been shown in our previous paper [2], while those obtained with methyl orange can be seen in Figure 4.

It is remarkable that the trends of the curves obtained by the competing methods, both with the two indicators and with benzoic acid, are qualitatively similar. The most interesting difference is that the effect of NaCl is opposite to the apparent stability constants of the complexes of phenolphthalein and methyl orange [2]. This fact itself and the large differences between effects of the different salts prove that the phenomena are caused not only by the changes in ionic strength. Further

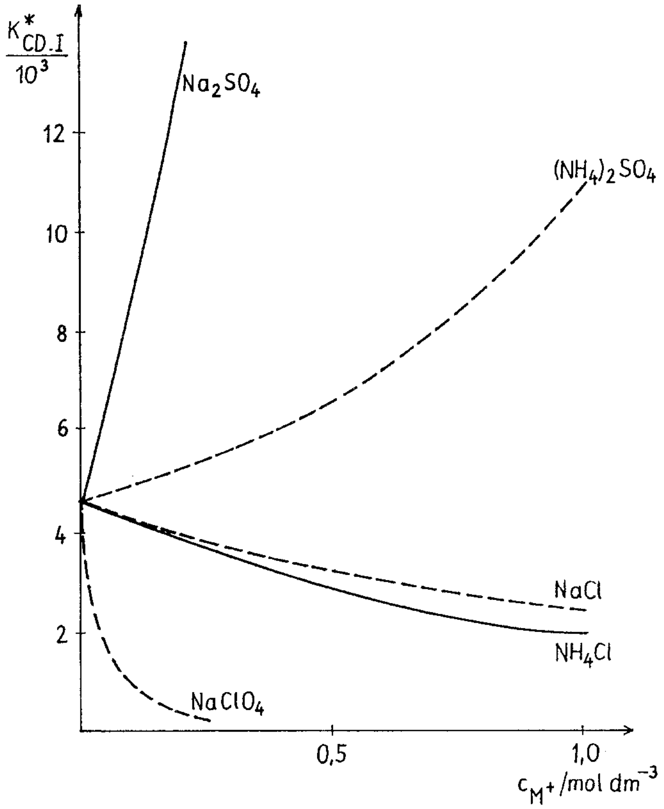

Fig. 4. The change of the apparent stability constants of β-CD–methyl orange complex in different electrolytes.

evidence are the results obtained in solutions containing two salts in constant total concentrations (see Figures 2 and 5).

4. Discussion

Comparing the different experimental results the first unambiguous conclusion that can be drawn is that the role of the anions is predominant in the interactions, that of the cations being less pronounced.

During the solubility measurements the solutions were always saturated with respect to one of the components, therefore these results cannot be adequately compared with those obtained in more dilute, homogeneous solutions. However, some qualitative conclusions can be drawn.

Based on the fact that the effect on the solubility (or on the precipitation) is always greater in the case of pure CD, it seems that the main interaction occurs between the anions and free CD. The compositions of the solid phases may be explained this way. In the absence of any salts the solubility of the free CD exceeds that of the CD-benzoic acid complex. The solubility of the free CD is significantly

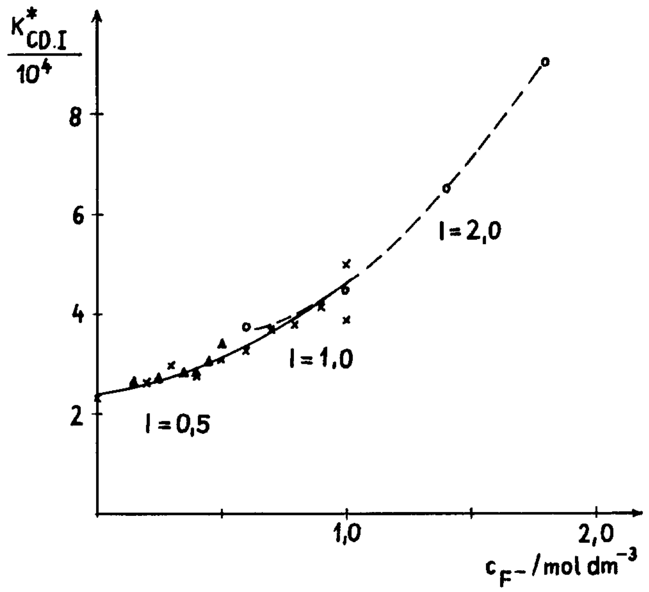

Fig. 5. The effects of ionic strength and F^-/Br^- exchange on the apparent stability constants of the β-CD–phenolphthalein complex. (At three different constant ionic strengths, where ▲: $I = 0.5$; ×: $I = 1.0$; ○: $I = 2.0$)

increased by perchlorate ions (better to say a significant amount is bound into a well soluble charged complex), therefore the benzoic acid complex can be crystallized only. In the presence of sulfate ions, however, the solubilities of the complex and free CD become closer, so both can be precipitated according to the composition of the solution.

The importance of intermolecular interactions and formation of mixed complexes is emphasised by the fact that sodium perchlorate is incorporated into the complex without decreasing its benzoic acid content. The drop in the solubility of the CD after a maximum in the presence of perchlorates can be explained by the formation and precipitation of CD–anion–cation complexes.

For a comprehensive interpretation, the following effects mentioned in the literature are considered: changes in the activity of water, formation of inclusion complexes and 'outer sphere' association.

Data for activity coefficients and activities of water can be found in compilation [12]. Comparing them with our results, it can easily be seen that even if some correlations exist in some cases, this effect cannot be the determining one (see also Figure 5).

Differences in changes of the activity coefficients or the activity of water depend first of all on the cations, while in our observations the role of the anions is predominant. Sometimes the solubility of the CD or the apparent stability constants of its complexes with the indicators are influenced in quite different ways by salts causing similar changes in the activity coefficients (e.g. NaCl and $NaClO_4$), and vice versa ($LiClO_4$ and $NaClO_4$). The role of the anions is also stressed by the fact that, if the ionic strength is constant, changing chloride ions for perchlorate causes a much greater change in the apparent stability constants than changing $NaClO_4$ for $LiClO_4$, while – as is known – the effect of lithium ions on the activity of water is unique.

The solubility of benzoic acid itself is significantly altered (mostly decreased, but to different extents) in solutions of different salts and this can be attributed to the decrease of the activity of water. Similar effects may contribute to the other phenomena, too, but if this were the determining factor, the formation of complexes with phenolphthalein and methyl orange could not be influenced in the opposite way by the same salt (NaCl), and the trends in the solubility changes of CD (caused by the different salts) are quite different.

The effect of sulfate ions are most in accordance with the changes in the activity of water: the apparent stability constants of the inclusion complexes are increased, the solubilities of benzoic acid, CD or benzoic acid–CD complex are decreased but the salt is not incorporated in the solid substances. However, the increase in the amount of the precipitated benzoic acid complex is not greater but smaller than that of the pure CD, and this can be explained only by the formation of quite soluble ternary complexes containing CD, benzoic acid and also sulfate ions. (The formation of a mixed complex with sulfate ion is also supported by the fact that the apparent stability constant of the CD–phenolphthalein complex is influenced similarly to the effect of sulfate ions by oxalate ions, too, which is most likely to form a hydrogen bonded chelate-like complex.)

The differences corresponding to the different cations beside the weak complexing chloride ions, especially the initial decrease in the solubility of CD in the presence of lithium and ammonium chloride (Figure 2), can also be attributed to changes in the structures of the solutions. However, the results obtained at constant ionic strengths suggest that LiCl in itself is the only case when the curvature (Figure 2) is caused merely by the change in the ionic strength.

The increase in the solubility of CD can be explained definitely by the formation of complexes between the CD and the components of the salts (first of all with the anions). Furthermore, the competing effects against the formation of complexes with the indicators and benzoic acid suggest inclusion type interactions.

Assuming simple competing reactions and only the formation of 1 : 1 complexes, stability constants can be calculated from the data of the photometric measurements in a simple way [9, 11]. The results obtained by the method using phenolphthalein and for salt concentrations of 0.1 mol dm^{-3} have been published in our previous paper [2].

The somewhat different results for the corresponding sodium, potassium, lithium or ammonium salts show the role of cations in the interactions, either by complex formation or by different changes caused in the activity of water. It must be mentioned that (i) in the latter case only, the effect of potassium and lithium ions should be of opposite sign (relative to that of the sodium salts), (ii) because of the relatively large excess of the salts the equilibrium concentrations of the anions and cations are practically equal to the analytical concentrations of the salts (and consequently to that of each other), in the case of formation of 1 : 1 complexes with the anions and the cations, too, the calculations give the sum of the two equilibrium constants.

The effect of chloride ions seems to be rather involved. The apparent stability constant of the phenolphthalein complex is increased but in 0.1 mol dm^{-3} concentration this remains on the limit of experimental errors [2]. Similarly, the slopes of the benzoic acid vs. CD-concentration plots are increased, while the solubility of benzoic acid itself is markedly decreased by NaCl. On the other hand, the solubility of pure β-CD is increased (Figure 1) and the apparent stability constant of the methyl orange complex is decreased (Figure 4) definitely indicating complex formation, and the formation of mixed complexes is proved by the incorporation of NaCl into the benzoic acid complex. As a conclusion, the interaction of NaCl with β-CD and its inclusion complexes must be regarded as the sum of 'salting out', formation of simple 1 : 1 complexes, CD-anion–cation complexes and mixed complexes as well.

Regarding the effect on the solubility increase of benzoic acid and on the phenolphthalein complex [2], the role of nitrates is opposite (and complicated), too, similarly to the chlorides and this suggests that also in the other (seemingly unambiguous) cases all these effects must be taken into account although one of them can be predominant. This is proved by the fact that broader concentration ranges can never be described properly by 1 : 1 complexes only, even if the ionic strength is constant (Figure 5). More complicated associates, too, must be considered, especially in describing the data of solubility measurements (CD : anion : cation = 1 : 1 : 0, 1 : 0 : 1, 2 : 1 : 0, 2 : 1 : 1 or species containing even more CD units) but the evaluation of such equilibrium constants (having very low values) would be very uncertain.

The formation of ternary complexes containing a relatively large organic guest molecule and some inorganic component at the same time is proved by the preparation of solid complexes in the presence of sodium chloride and sodium perchlorate and it is very probable with sulfate ions, too, according to the equilibrium studies in solutions. The small chloride ions, perhaps, may be inserted together with the larger guest. An 'outer sphere' type attachment, however, seems to be more probable (based on the composition of the CD-benzoic acid complex crysallized from $NaClO_4$ solutions) and this is in accordance with the suggestions of Rohrbach [5] and Høiland [8]. Considering that these anions may act as bridging ligands in other complexes, too, perchlorate ion is very likely to link two molecules of β-CD or of its inclusion complex. These connections must be realized through hydrogen bonds with the OH groups of the CD (or water molecules can also be involved).

5. Summary

i. In the interactions between β-cyclodextrin and inorganic salts the participation of anions is predominant. Dilute solutions can be characterized satisfactorily by the formation of 1 : 1 CD-anion complexes, at higher concentrations more complicated species (containing cations as well) are also formed.

ii. Changes in activity coefficients or in the activity of water may also influence the interactions but this effect is only of minor importance.

iii. Based on these investigations it cannot be decided unambiguously whether the anions form real inclusion complexes or are attached (to the CD) from outside by hydrogen bonds. Most probably both types of interaction occur, depending on the circumstances.

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